FDA Questions for Circulatory System Devices Panel

June 13, 2012

P110021 – Edwards SAPIEN Transcatheter Heart Valve (THV)

Background

The Kaplan-Meier (K-M) estimates of the all cause mortality rate at 1 year are summarized in the table below. These rates are stated to be 24.27% and 26.80% for the pooled TAVR (treatment) and AVR (control) arms, respectively. The survival difference (TAVR-AVR) was 0.0253, and the 95% one-sided lower confidence limit (CL) for the difference was -0.0299, which is greater than the pre-defined non-inferiority margin (-0.075). The p-value for the non-inferiority test is 0.0014, indicating that the primary endpoint is met with a 0.075 non-inferiority margin.

In the Intent-To-Treat (ITT) cohort for the transfemoral subgroup, the KM event rates at 1 year are 22.24% and 26.36% for the transfemoral treatment group and control group, respectively. The survival difference is 4.12% (Transfemoral-control). The 95% one-sided lower CL for the survival difference is -2.34%. In the As-Treated (AT) cohort for the transfemoral subgroup, the KM event rates at 1 year are 21.35% and 25.18% for the transfemoral treatment group and control group, respectively. The survival difference is 3.83% (transfemoral-control). The 95% one-sided lower CL for the difference is -2.68%.

In the ITT cohort for the transapical subgroup, the KM event rates at 1 year are 29.04% and 27.86% for the transapical treatment group and control group, respectively. The survival difference is -1.18% (transapical-control). The 95% one-sided lower CL for the difference is -11.69%. In the AT cohort of the transapical subgroup, the KM event rates at 1 year are 29.07% and 25.28% for the transapical treatment group and control group, respectively. The survival difference is -3.79% (transapical-control). The 95% one-sided lower CL for the difference is -14.29%.

Table 1 - Kaplan-Meier Rates for Pooled and Subgroup Cohorts

Cohort Identification	K-M 1-Year Rate	Lower CL
Pooled TAVR	24.27%	-0.0299%
Pooled AVR	26.80%	
ITT Transfemoral TAVR	22.24%	-2.34%
ITT Transfemoral AVR	26.36%	
AT Transfemoral TAVR	21.35%	-2.68%
AT Transfemoral AVR	25.18%	
ITT Transapical TAVR	29.04%	-11.69%
ITT Transapical AVR	27.86%	
AT Transapical TAVR	29.07%	-14.29%
AT Transapical AVR	25.28%	

When evaluating whether or not the results of the trial support the safety and effectiveness of the SAPIEN THV for the proposed indications, we ask the Panel to address the following questions.

Safety

It appears that patients treated with the SAPIEN Heart Valve System had an increase in strokes perioperatively compared to the control group treated with AVR. These events may have been under-reported, since detection was based on identification of symptoms, and not rigorous neurological evaluations. Additionally, the stroke rate in the non-randomized continued access protocol (CAP) cohort appears to have decreased for reasons that are unclear.

Q1a. Please comment on the problems of stroke ascertainment in this trial.

Q1b. Please discuss whether you think that the antithrombotic regimen for this device and procedure are sufficiently understood and if a specific protocol is necessary.

Q1c. Please provide any other thoughts you have for mitigating stroke.

Q1d. Please comment on the CAP results, particularly as they apply to stroke results noted in the transapical patients.

Increasing evidence, including evidence from this trial, demonstrates the association between mild or greater aortic regurgitation and one year and longer-term mortality in TAVR patients. It is noted that 53% of the SAPIEN patients in the randomized trial had mild or greater aortic insufficiency and mild or greater aortic insufficiency appears correlated with poorer long term outcome.

Q1e. Please comment on the implications of the aortic insufficiency results.

It appears that patients treated with the SAPIEN Transcatheter Heart Valve had an increase in major vascular complications compared to the control AVR group.

Q1f. Please comment on these results and any suggestions you might have for lowering the rate of vascular complications.

Trial Conduct

There are a variety of factors that could have resulted in introduction of bias or could have confounded analysis in this study. In particular, the number of AVR patients not receiving AVR (10.8%) and those having an important delay in treatment (49 AVR patients and 20 TAVR patients, see breakdown in table below), the number of TAVR patients receiving AVR (11 patients), the AVR patients that underwent concomitant operations (total of 12.8%), and site variability in patient selection make evaluation of the data in this trial challenging.

Table 2 - Delay Between Randomization and Treatment

Group	# Patients with ≥30 day delay	# Patients with delay 30-50 days	# Patients with delay 51-90 days	# Patients with delay >91 days
AVR/Control	49	35	12	2
TAVR/Teat	20	16	2	2

Q2a. Please discuss the impact of these trial conduct issues on the overall interpretation of the data.

Q2b. Please discuss how we may better address significant trial conduct issues in the future for this class of devices.

Implantation Approach

The all-cause mortality rates for the subgroups are described in the introduction above.

The two tables below present the stroke rates. The first table contains the rates for the randomized PARTNER trial (pooled, and by treatment approach in both the ITT and the AT cohorts), and the second table compares rates to those found in the non-randomized Continued Access study (NRCA).

Table 3 - One and Two Year Kaplan-Meier Stroke Rates*

Cohort Identification	K-M 1-Year Stroke Rate	K_M 2-Year Stroke Rate
ITT Pooled TAVR	6.0	7.7
ITT Pooled AVR	3.2	4.9
AT Pooled TAVR	5.8	7.5
AT Pooled AVR	3.0	4.4
ITT Transfemoral TAVR	4.6	5.7
ITT Transfemoral AVR	2.3	2.9
AT Transfemoral TAVR	3.8	5.0
AT Transfemoral AVR	1.4	2.0
ITT Transapical TAVR	9.6	12.6
ITT Transapical AVR	5.4	9.9
AT Transapical TAVR	10.8	13.8
AT Transapical AVR	7.0	10.0

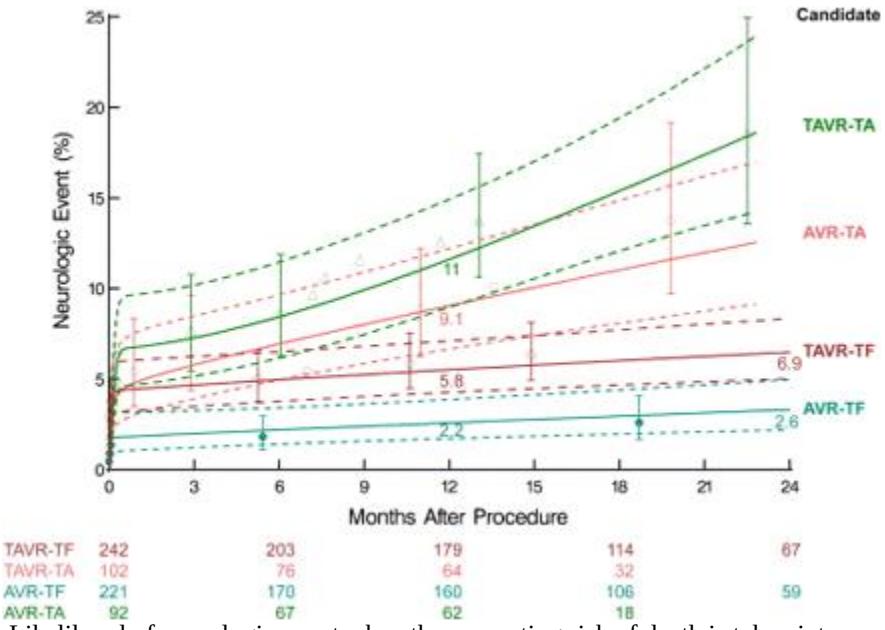
* These rates ignore competing risk
ITT – Intent-To-Treat
AT = As-Treated

Table 4 - Stroke in RTC and CAP Studies

		≤ 30 Days			31 Days – 1 Year		
	Patients in Group	Number of Events	Patients with Event	KM Event rate at 30 Days	Number of Events	Patients with Event	KM Event rate at 1 Year
Stroke							
NRCA –TA	843	17	16	2.0%	6	6	3.7%
Randomized TAVR – TA	104	6	6	5.8%	3	3	9.6%
NRCA TF	745	29	28	3.9%	10	10	5.8%
Randomized TAVR - TF	244	10	10	4.1%	1	1	4.6%

NRCA = non-randomized continued access patients
TA = transapical
TF = transfemoral

Miller et al modeled combined stroke (N = 34) and TIA (N= 15) data from the RCT in a recent publication in the Journal of Thoracic Cardiovascular Surgery (Miller, et al. J Thorac Cardiovasc Surg 2012; 143:832-43). In the article, both stroke and TIA are presented together as neurological events (y-axis below) for the different subgroups.



Likelihood of neurologic event when the competing risk of death is taken into consideration in each of the 4 treatment subgroups. Depicted in light blue is the curve for the likelihood of a neurologic event after aortic valve replacement (AVR) in the TF stratum (AVR-TF), the salmon-colored curve is that for AVR patients assigned to the TA stratum (AVR-TA), the brown curve is for the transfemoral transcatheter aortic valve replacement patients in the TF stratum (TAVR-TF), and the green curve is for the TAVR patients in the transapical stratum (TAVR-TA). Number of patients at risk is denoted below the horizontal axis at 6-month intervals. [Miller, et al. J Thorac Cardiovasc Surg 2012;143:832-43]

Figure 1. Neurologic Events after Procedure

Q3. Please specifically comment on the safety and effectiveness results for the transapical approach.

Proposed Indications for Use

The proposed Indications for Use Statement to be included in the labeling reads as follows (the bolded phrases were added by FDA after sponsor concurrence was obtained):

TRANSFEMORAL PROCEDURE

The Edwards SAPIEN Transcatheter Heart Valve, model 9000TFX, sizes 23 mm and 26 mm, is indicated for patients with severe symptomatic native aortic valve stenosis who have been examined by **a heart team including** a cardiac surgeon and found to be:

- inoperable and in whom existing co-morbidities would not preclude the

expected benefit from correction of the aortic stenosis, or

- operable candidates for aortic valve replacement but who are at a greater than **or equal to** 15% (high) risk of mortality for surgical aortic valve replacement.

The RetroFlex 3 Delivery System is indicated for the transfemoral (TF) delivery of the Edwards SAPIEN Transcatheter Heart Valve.

The RetroFlex Balloon Catheter is indicated for valvuloplasty of a stenotic cardiac valve prior to implantation of the Edwards SAPIEN transcatheter heart valve.

The Crimper is indicated for use in preparing the Edwards SAPIEN Transcatheter Heart Valve for implantation.

TRANSAPICAL PROCEDURE

The Edwards SAPIEN Transcatheter Heart Valve, Model 9000TFX, sizes 23 mm and 26 mm, is indicated for transapical (TA) delivery in patients with severe symptomatic native aortic valve stenosis who have been examined by **a heart team including** a cardiac surgeon and found to be operative candidates for aortic valve replacement but who are at a greater than **or equal to** 15% (high) risk of mortality for surgical aortic valve replacement.

The Ascendra Balloon Catheter is indicated for the transapical delivery of the Edwards SAPIEN Transcatheter Heart Valve.

The Ascendra Balloon Aortic Valvuloplasty Catheter is indicated for valvuloplasty of a stenotic native aortic valve prior to implantation of the Edwards SAPIEN transcatheter heart valve.

The Ascendra Introducer Sheath Set is indicated for the introduction and removal of interventional devices used with the Edwards SAPIEN Transcatheter Heart Valve.

The Crimper is indicated for use in preparing the Edwards SAPIEN Transcatheter Heart Valve for implantation.

Q4. Please provide any suggested major changes to the indications for use that better describe patient population and/or intended use.

<u>Gender</u>

FDA performed a *post* hoc gender analysis of the primary endpoint. There appear to be suggestions of a clinically important gender difference in the mortality endpoint in this study. All-cause mortality was numerically higher in the TAVR arm than that in the AVR arm for males. The mortality rates at 1 year are 28.52% and 25.21% for TAVR and AVR, respectively, in the ITT population. The mortality rates at 1 year are 27.44% and 22.67% for TAVR and AVR, respectively, in the AT population (non-inferiority was not met). For females, the

mortality rates at 1 year are 18.45% and 29.03% for TAVR and AVR, respectively, in the ITT population. The mortality rates at 1 year are 18.58% and 28.56% for TAVR and AVR, respectively, in the AT population. In the CAP study, at one year, the K-M estimated event rates in ITT population are 18.54% for females and 25.94% for males, respectively. Those numbers are numerically close to those observed in the randomized study.

Table 5 - Mortality Analysis by Gender

Cohort Studied	**Males**		**Females**	
	ITT	**AT**	**ITT**	**AT**
TAVR PARTNER RCT	28.52%	27.44%	18.45%	18.58%
AVR PARTNER RCT	25.21%	22.67%	29.03%	28.56%
TAVR CAP	25.94%		18.54%	

Q5. Please comment on interpretation of the results across genders.

Valve Performance and Durability

The average follow-up for the primary endpoint in the data presented in this study was 1.6 ± 1.0 years for the pooled AVR and 1.8 ± 1.0 years for the TAVR cohorts. Additional data out to 2 years were presented for certain endpoints. Although there are some limited data beyond 2 years from the PARTNER trial and the long-term durability of the SAPIEN THV remains unclear.

Q6a. Please comment on the data currently available for long-term durability of the SAPIEN Heart Valve.

Literature has reported many cases of valve-in-valve implantation involving the SAPIEN valve, including SAPIEN in SAPIEN, SAPIEN in another transcatheter valve, and SAPIEN in a previously implanted surgical bioprosthesis. There are limited data supporting device durability and performance when implanted in this manner. Corrosion due to increased contact between metals of 2 valves may result in a decrease in durability of the valve. Once commercially available, it is possible that valve-in-valve use of the SAPIEN may occur at a higher frequency.

Q6b. Please comment on possible risk mitigation measures that should be taken to address the safety and effectiveness of using the Valve-In-Valve technique.

Q6c. Please provide comment on whether you think the use of Valve-In-Valve technique can be addressed in the labeling.

Informed Consent

Percutaneous heart valve implantation is different from standard cardiac valve surgery in many important ways. FDA is interested in ensuring that patients are well-informed about the risks and benefits of both procedures before making a decision.

One approach the Agency has considered to improve the typical informed consent process is recommending a standard section in the informed consent document that details the potential risks and benefits that may be associated with the SAPIEN Transcatheter Heart Valve. Both the

patient and the physician would then have to sign off on this section in front of a witness to ensure adequate informed consent.

Q7a. Please comment on the need for a more detailed informed consent form in general.

Q7b. Please comment on the appropriateness of requiring such a form given in the example above for the SAPIEN Transcatheter Heart Valve patients.

Overall Safety and Effectiveness

Q8. Please comment on whether you believe the totality of the data presented and discussed demonstrates a reasonable assurance of safety and effectiveness for the SAPIEN Transcatheter Heart Valve in the intended patient population.

Post-Approval Study

Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for pre-market approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable. The questions included below, regarding potential post-approval studies, are for the Panel to include in the deliberations. Panel PAS recommendations will be taken into account if FDA finds the device approvable based upon the clinical premarket data.

Q9a. Please comment on whether or not the relationship between mortality and aortic regurgitation severity (no/trace versus mild/moderate/severe) within TAVR patients should be monitored in the PAS.

Q9b. Please comment on whether or not the PAS should be used to monitor short-term and long-term effects of safety and effectiveness of valve-in-valve implantation.

Q9c. Please comment on any additional endpoints that should be incorporated into the PAS.

Labeling

The Sponsor provided draft labeling in the panel pack.

Q10. Please comment on the appropriateness of the study data included in the labeling, and discuss whether there are any analyses or data not provided that would be important to provide to the user in the labeling.